REMARKS

Reconsideration and reexamination of this application are respectfully requested.

A. Status of Claims

Claims 71, 76, and 77 are amended. Claims 71-77 are pending and stand rejected.

The amendments to claims 71, 76, and 77 specify that the first gene product is "a receptor," "an interferon," and "an interleukin," respectively. Those claims have also been amended to delete "part or all of." Together, the plain meaning of that amended claim language necessarily requires the presence of a complete and functional protein product. Thus, "the first heterologous insertion DNA sequence" in each of those claims necessarily is a sequence that encodes a complete and functional protein product of the recited type, and not a mere nonfunctional fragment.

The claims as amended are fully supported in the specification as filed at least because the plain wording of the specification discloses embodiments in which the complete and functional recited classes of proteins are used.

B. Withdrawn Rejections

Applicant thanks the Examiner for withdrawing the prior rejections under 35 U.S.C. § 112, first and second paragraph, and the rejections under 35 U.S.C. § 103(a) that relied on the Mansour reference. As the Examiner has acknowledged, Mansour is not prior art to this application.

C. Maintained Rejections Under 35 U.S.C. § 103(a)

Various groupings of claims 71-77 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nandi et al., *Proc Natl Acad Sci USA.*, Vol. 85, No. 11, pp. 3845-3849 (1988) ("Nandi"), in combination with various other references. Action at Items 9-13. Applicant respectfully traverses those rejections.

In responding to Applicant's prior arguments, the Examiner stated that [i]t is worth noting that the limitation 'the first heterologous insertion DNA sequence encodes a fist gene product that does not confer resistance to a selection agent involved in the selection of transformants' reads on any transcription product (RNA) and translation product (protein), either before or after recombination event occurs." (Office Action at page 14.) Then, comparing that language to the disclosure of Nandi, the Examiner stated that "[i]n this regard, the truncated transcription product (RNA) and truncated translation product (protein) expressed by the $\Delta\beta$ sequences after recombination event is certainly encompassed by the limitation." (*Id.*) The Examiner then asserted that "the claims do not require the gene product to be complete or functional. Since there is no requirement for the inserted DNA to be genomic DNA, and [since it] can be a cDNA, the term 'gene product' is anything encoded by the 'gene'." (*Id.* at pages 14-15.) Applicant respectfully disagrees and submits that the Examiner's assertions do not apply to the amended claims.

As amended, the claims require that the first heterologous insertion DNA sequence encodes a complete and functional protein product of the type recited in each of claims 71, 76, and 77, and not a mere nonfunctional fragment. Furthermore, the claim language makes clear that the full first heterologous insertion DNA sequence is

present in the vector as claimed and that the vector is designed such that the full first heterologous insertion DNA sequence is also present in the genomic DNA following integration into the genome of the vector by homologous recombination, by reciting:

> wherein, upon introduction of the DNA construct into the mammalian cell, the first flanking DNA sequence recombines with the homologous first endogenous DNA sequence in the genome of the mammalian cell, and the second flanking DNA sequence recombines with the homologous second endogenous DNA sequence in the genome of the mammalian cell, such that the first and second heterologous insertion DNA sequences are inserted into the genome of the mammalian cell between the first and second endogenous DNA sequences.

That language defines the vector as containing two sequences homologous to the sequences within the recipient gene. Both homologous sequences flank the heterologous insertion sequences. These are the features of a replacement-type vector which promotes two homologous recombination events between each of two sequences within the recipient gene and their homologous two sequences flanking the DNA sequence to be inserted in the vector.

As Applicant argued in the prior response, Nandi does not disclose a vector construct with these features.

Instead, the vector disclosed in Nandi (p ΔB117, from Smithies et al., *Nature* 1985 fig 1b), contains a unique homologous sequence (including part of the *B* gene). This vector is cut within the unique homologous sequence to promote one homologous recombination event triggering the integration of the entire vector including the homologous sequence carried by the vector leading to duplication of β globin gene sequences (Nandi, Figure 1a). These vectors are called insertion-type vector because

they perform the insertion of the entire vector. Insertion type and replacement type vectors differ in their structure and for that reason take part in different types of homologous recombination pathways as described above.

The remaining references cited by the Examiner disclose various gene products. The Examiner asserts that the skilled artisan would have replaced the $\Delta\beta$ sequences of the Nandi vector, which encode at most a protein fragment and are used in the Nandi vector as homologous sequences, with the gene products of the other references. Applicant respectfully disagrees and submits that the Examiner has not established a *prima facie* case of obviousness.

The Office has pointed to nothing in the disclosure of Nandi, or any other reference, that suggests or motivates the skilled artisan to modify the vectors disclosed in Nandi so as to **further comprise** a first heterologous insertion DNA sequence that encodes a complete and functional protein product of the type recited in each of claims 71, 76, and 77, and not a mere nonfunctional fragment.

A further indication that no *prima facie* case of obviousness is present is provided by the recognition in the art at the time Applicant made the invention, that success was not expected in following the path taken by Applicant. Specifically, the proper inquiry is whether one of ordinary skill in the art, as of March 20, 1989, the effective filing date of the claims, would have reasonably expected that the second insertion DNA sequence (as claimed by Applicant) could be modified by combining with it, in the same vector, a first insertion DNA sequence (as defined by Applicant's claims). The evidence establishes that the answer to that question is a resounding no.

In October 1990, a full one and a half years **after** Applicant's effective filing date, Mansour et al. published a paper describing a process for providing a recombinant heterologous gene in the genome of a eukaryotic cell, utilizing a transfection vector which comprises a heterologous DNA sequence that comprises a first insertion DNA sequence and a second insertion DNA sequence, as required by the new claims. (Exhibit A, Mansour et al., "Introduction of a LacZ Reporter Gene into the Mouse int-2 Locus by Homologous Recombination," *Proc. Natl. Acad. Sci. USA*, Vol. 87, pp. 7688-92 (1990).) Specifically, the heterologous DNA sequence of the vectors of Mansour comprises a first insertion DNA sequence that comprises a first coding sequence that encodes a first product that is a complete and functional protein product that does not confer resistance to a selection agent involved in the selection of transformants (lacZ), and a second insertion DNA sequence that comprises a second coding sequence that encodes a second product that confers resistance to a selection agent involved in the selection of transformants (neomycin), and a promoter allowing the expression of said second product in a mouse embryonic stem cell. Thus, similarly to claims 71, 76, and 77—but in contrast to Nandi—Mansour describes a construct in which the first insertion DNA sequence encodes a first product that is a complete and functional protein product that does not confer resistance to a selection agent involved in the selection of transformants.

Mansour described the state of the prior art leading up to their work as reflecting a

> common[] belie[f] that the frequency of gene targeting events in mammalian cells is inversely proportional to the length of nonhomologous DNA sequences that are transferred to the

> chromosomal target (4-7). This belief is based in part on the observation that in cultured mammalian cells, the frequency of intrachromosomal gene conversion is inversely proportional to the length of nonhomologous DNA converted in the recipient DNA sequence (8).

(Monsour. at page 7688, left column.)

In a first set of experiments, Mansour challenged this belief of the art by performing homologous recombination experiments in which the *hprt* gene was disrupted by insertion of heterologous DNA inserts of 8 bp, 1kb, and 3.4 kb. (*Id.* at page 7689, left column.) The authors also noted that "[i]n addition to this study of heterologous inserts in the eighth exon, [they had] also examined the effect of heterologous inserts of 4.3 kb and 12 kb in the third exon on the *hprt* targeting frequency [and that] . . . comparable targeted disruption frequencies were also obtained with these *hprt* vectors" (*Id.* at page 7689, right column.) The authors concluded that those results "demonstrated that the frequency of gene targeting is not influenced by the length of nonhomologous DNA sequences transferred to the target chromosomal locus" as the result of the homologous recombination event. (*Id.* at page 7691, last full sentence.) In light of this, the authors observed that "[a]s a result of this finding, a wider spectrum of designed genomic alterations **is now feasible**." (*Id.* at pages 7691-92, bridging sentence; emphasis added.)

Mansour described this finding—that the frequency of gene targeting is not influenced by the length of nonhomologous DNA sequences transferred to the target chromosomal locus—as an "unexpected observation." (*Id.* at page 7688, left column.) As an "initial test of this unexpected observation," Mansour "introduced 5.4 kilobases (kb) of nonhomologous DNA containing the genes which encode β-galactosidase (β-

gal) and neomycin resistance (*neo*^{R}) into one of the endogenous *int-2* alleles in an ES cell line" using homologous recombination. (*Id.* at page 7688, left column.) It is this disclosure of Mansour that is encompassed by the new claims.

If the skilled artisan would have expected success in making Applicant's invention, then Mansour would not, one and a half years later, describe the results of their experiments doing just that as "an initial test of an unexpected observation." Instead, Mansour makes it abundantly clear that the initial observation—that the frequency of gene targeting is not influenced by the length of nonhomologous DNA sequences transferred to the target chromosomal locus—is an "unexpected observation," on which the subsequent experiment—in which 5.4 kilobases (kb) of nonhomologous DNA containing the genes which encode β-gal and *neo*^{R} was inserted into one of the endogenous *int-2* alleles in an ES cell line using homologous recombination—was based. Critically, it is an observation that was not available to the skilled artisan as of March 20, 1989.

For the above reasons, Applicant submits that the new claims are nonobvious over Nandi alone or in combination with the other cited references.

D. Conclusion

Applicant respectfully requests that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 71-77 in condition for allowance. Applicant submits that the proposed amendments of claims 71, 76, and 77 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were earlier claimed

and the amendment merely narrows the scope of the claims in response to an issue raised by the Examiner. Therefore, this Amendment should allow for immediate action by the Examiner.

Finally, Applicant submits that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

If there is any fee due in connection with the filing of this Reply, please charge the fee to our Deposit Account 06-0916.

Respectfully submitted,

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